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EXAMINER				
HUYNH, PHUONG N				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/588,220

Applicant(s)

RONIN ET AL.

Examiner

PHUONG HUYNH

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 101-113 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 101-113 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 August 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/5506)
- Paper No(s)/Mail Date 8/2/06
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. Claims 101-113 are pending.
2. The request for reconsideration and withdrawal of the election species requirement in view of the claims amendment is acknowledged.
3. In view of the claims amendment filed February 4, 2009, the species restriction mailed February 4, 2009 between various glycosylation states of second glycoprotein is hereby withdrawn.
4. Claims 101-113, drawn to a process for screening glycoform specific antibodies among antibodies directed against a first glycoprotein which is pituitary or blood human TSH that read on glycosylation state essentially more sialylated, more branched and less fucosylated, are being acted upon in this Office Action.
5. The International Search Report in the IDS filed August 26, 2006 has been considered but crossed out because said search report is inappropriate to be printed on an issued patent.
6. Claim 101 is objected to because misspelled "TSR". It should have been "TSH".
7. Claims 104 is objected to because of improper Markush group "...selected from the group comprising ...**or** sialic acid-specific... lectin". Specifically, "or" should have been "and". Further, the term "selected from the group comprising" should have been "selected from the group consisting of ..." One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925).

When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper. Correction is required.

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8. Claim 105 is objected to because of improper Markush group "...selected from the group *comprising* ...**or** glycosyltransferase, in particular a sialyltransferase". Specifically, "or" should have been "and". Further, the term "selected from the group *comprising*" should have been "selected from the group consisting of ..." Finally, the phrase "in particular" is indefinite, improper and failing to conform to current U.S. practice.

9. Claims 112-113 are objected to because the phrase "in particular" is indefinite, improper and failing to conform to current U.S. practice.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 101-113 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. **This is New Matter.**

Neither the specification nor the claims as originally filed provide written support for any pituitary or blood human "TSR" for the claimed method.

The specification discloses *screening* glycoform specific antibodies that bind to human TSH. As such, applicants are not in possession of a process of screening glycoform specific antibodies among antibodies elicited against any first pituitary or blood human "TSR" and binding between any recombinant human "TSR".

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 110-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 101 is incomplete for failing to achieve the goal set forth in the preamble. The preamble of claim 1 recites a process for *screening* glycoform specific antibodies and ends with

"producing antibodies capable of binding to at least one given glycoform of the second glycoprotein". Further, it is unclear how the binding of antibodies to various glycoforms specific recombinant TSH related to the binding of antibodies to pituitary or blood (circulating) human TSH.

Claims 102-113 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

The "TSR" in claim 1 is indefinite because "TSR" stands for thrombospondin type 1 repeats (TSR). Neither the specification nor the claims provide adequate guidance to the interpretation of such term. The specification discloses only TSH. Further, while abbreviation can be used in a claim, to avoid potential confusion, the first recitation of the abbreviation should be preceded by the full terminology, such as human thyrotropin or thyroid stimulating hormone (TSH), for example.

Regarding claims 104, 109, 112, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The "preliminary step" in claim 110 has no antecedent basis in base claim 103. Base claims 103 and 101 do not recite "preliminary step" for the claimed method.

The "preliminary step" in claim 111 has no antecedent basis in base claim 101. Base claim 101 does not recite "preliminary step" for the claimed method.

The phrase "if adequate" in claim 113 is indefinite because the metes and bounds of what would constitute "adequate" cannot be determined. Such term is relative and neither the specification nor the claims provide adequate guidance to the interpretation of such term.

Claim 113 is indefinite because it is unclear the binding specificity of capture antibody, and the tracer antibody.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
16. Claims 101-108 and 110-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papandreou et al (Molecular and Cellular Endocrinology 73: 15-26, 1990; PTO 1449) in view of Kashiwai et al (J Immunological Methods 143: 25-30, 1991; PTO 1449), Schaaf et al (Molecular and Cellular Endocrinology 132: 185-194, 1997; PTO 1449), and Szkudlinski et al (Endocrinology 133(4): 1490-1503, 1993; PTO 1449).

Papandreou et al (Molecular and Cellular Endocrinology 73: 15-26, 1990; PTO 1449) teach a process of screening glycoform specific antibodies directed against native human TSH (first glycoprotein) and deglycosylated human TSH (second glycoprotein being itself less glycosylated form of first glycoprotein) (see entire document, page 18, in particular) or glycosylated TSH (see page 23, col. 1, in particular). Papandreou et al teach the importance of noting among the glycosylation-dependent epitopes of TSH antibodies in assaying biologically active TSH in human blood samples (see paragraph bridging page 2425, in particular). Papandreou et al teach loss of hTSH immunoreactivity is caused by profound alteration of the conformation of hTSH caused by deglycosylation which may very well have clinical relevance in assaying TSH in human blood samples (see page 24, col. 2, last paragraph, in particular). The reference antibodies to be screened are classified in pools based on the binding specificity and epitopes (see Table 1, Fig 1, in particular). It is within the purview of one of ordinary skill in the immunology art to determine antibody binding in series such that antibodies from the same pool cannot bind to same TSH at the same time.

Papandreou et al does not teach the process of screening glycoform specific TSH antibodies wherein the second TSH is a recombinant human TSH produced by mammalian cells, and the state of glycosylation of said recombinant hTSH is such that it is more sialylated, more branched and less fucosylated.

However, Kashiwai et al teach a method of screening antibodies that recognize recombinant human thyrotropin produced by mammalian cells such as Chinese Hamster Ovary Cells (see page 26, col. 1, recombinant hTSH, in particular) and compared the binding of such antibodies with that of the pituitary derived reference human TSH (first glycoprotein) (see entire document, abstract, in particular). Kashiwai et al teach the availability of rhTSH will be a good candidate for a future standard material in assays for hTSH (see abstract, in particular). The binding of antibodies to native TSH and rhTSH variants such as rhTSH-G and rhTSH-S are determined by ELISA (see page 27, col. 1, Immunoassay, in particular).

Schaaf et al teach a method of producing recombinant human thyrotropin (rhTSH) by mammalian cells such as Chinese Hamster Ovary Cells (CHO) or Cos cells and the glycosylation variants of such rhTSH are compared to that of the human pituitary TSH (see entire document, page 186, col. 1, in particular). Schaaf et al teach the degree of glycosylation such as sialylation as determined by neuraminidase treatment (see page 186, col. 2, paragraph 2.2, in particular), branching as determined by ConA chromatography (see page 186, col. 2, last paragraph, in particular) and fucosylation as determined by lentil chromatography (see page 187, col. 1, paragraph 2.5, page 189, col. 2, in particular). Schaaf et al teach neuraminidase treatment (desialylated) or sialylated hTSH isoforms did not show any difference in bioactivity in Cos-7 cell. However, sialylated and desialylated TSH samples produced by CHO cells showed higher potency in stimulating cAMP, which may reflect on different posttranslational processing of the hTSH in different cell lines. Schaaf et al teach high mannose TSH variant (firmly bound to ConA due to their branching property of N-linked oligosaccharide) showed greater potency in stimulating cAMP formation and IP-release by both cell lines (see abstract, page 192, col. 2, in particular). Schaaf et al teach core-unfucosylated TSH variants (less fucosylated and lentil-unbound TSH) proved to be a strong stimulator of cAMP release by CHO and Cos cells (see abstract, in particular). Claim 107 is included in this rejection because ConA fractionation of recombinant is performed by collecting three fractions such as unbound fraction, weakly bound versus firmly bound fraction (see page 188, col. 2, first paragraph, page 189 col. 1, in particular).

Szudlinski et al teaches a method of producing recombinant human thyrotropin (rhTSH) by mammalian cells such as Chinese Hamster Ovary Cells to overcome the limitation of purifying human TSH from the serum (see page 1491, col. 2, in particular). Szudlinski et al teaches a process of determining the glycosylation state of the rhTSH such as sialylation state and/or

fucosylation state of rhTSH (see page 1494, Table 2, carbohydrate composition analysis, page 1496, in particular). Szudlinski et al teach glycosylation patterns appear to affect the antigenic structure of secreted (blood) glycoprotein hormone such as rhTSH and in vivo half life of such hormone (see page 1499, col. 1, in particular). Szudlinski et al teach recombinant produced human TSH (rhTSH) and sialic acid was relatively high in the rhTSH-G preparation compared with the pituitary derived human TSH (phTSH) (see col. paragraph bridging page 1494-1495, in particular). Szudlinski et al teach neuraminidase treatments eliminated rhTSH-G heterogeneity in chromatofocusing and sialylation appears to be one of the main determinants of rhTSH charge heterogeneity (see page 1499, col. 2, second paragraph, in particular). Szudlinski et al teach high degrees of sialylation always correspond to significant longer half-life and in vivo bioactivity (see page 1499, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skilled in the art at the time the invention was made with the expectation of success to screen antibodies for binding to different glycoforms of human TSH of Papandreou et al with the recombinant human thyrotropin produced by mammalian cells such as Chinese Hamster Ovary Cells by comparing the binding of such antibodies with that of the pituitary derived reference human TSH as taught by Kashiwai et al where the glycoform specific rhTSH is more sialylated as determined by enzymatic modification such as neuraminidase treatment or sialyltransferase treatment, highly bound to ConA (highly branched) and less fucosylated as determined by (lentil-unbound TSH) as taught by Schaaf et al and Szudlinski et al.

One of ordinary skill in the art would have been motivated with the expectation of success to screen antibodies that bind to various recombinant human TSH and glycoform variants thereof by compared to that of the native human TSH because Papandreou et al teach the glycosylation-dependent epitopes of TSH antibodies are important in assaying biologically active TSH in human blood samples and pituitary derived human TSH (see paragraph bridging page 2425, in particular).

One of ordinary skill in the art would have been motivated with the expectation of success to do this because Szudlinski et al teach glycosylation patterns appears to affect the antigenic structure of secreted (blood) or circulating rhTSH, in vivo half life and/or bioactivity of such glycoprotein hormone (see page 1499, col. 2, in particular).

One of ordinary skill in the art would have been motivated with the expectation of success to screen antibodies that bind to various recombinant human TSH and glycoform variants thereof by compared to that of the native human TSH because of the potential different posttranslational processing of the hTSH produced in different cell lines as taught by Schaaf et al (see abstract, in particular).

One of ordinary skill in the art would have been motivated with the expectation of success to screen antibodies that bind to various recombinant human TSH and glycoform variants thereof by compared to that of the native human TSH because high degrees of sialylation always correspond to significant longer half-life and in vivo bioactivity as taught by Szudlinski et al (see page 1499, col. 2, in particular). Claim 102 is included in this rejection because the reference antibodies that bind to recombinant pituitary human TSH various also bind to native pituitary human TSH with equal affinity.

17. Claim 109 is rejected under 35 U.S.C. 103(a) as being unpatentable over Papandreou et al (Molecular and Cellular Endocrinology 73: 15-26, 1990; PTO 1449) in view of Kashiwai et al (J Immunological Methods 143: 25-30, 1991; PTO 892), Schaaf et al (Molecular and Cellular Endocrinology 132: 185-194, 1997; PTO 1449) and Szkudlinski et al (Endocrinology 133(4): 1490-1503, 1993; PTO 1449) as applied to claims 101, 103-108 and 110-112 mentioned above and further in view of Legaingneur et al (J Biol Chem 276(24): 21608-21617, 2001; PTO 1449).

The combined teachings of Papandreou et al, Kashiwai et al, Schaaf et al, and Szkudlinski et al have been discussed supra. Szkudlinski et al teach high degrees of sialylation always correspond to significant longer half-life and in vivo bioactivity (see page 1499, col. 2, in particular).

The invention in claim 109 differs from the teachings of the references only in that the process of screening glycoform specific antibodies among antibodies elicited against recombinant human TSH wherein the sialyltransferase is a α -2,6-sialyltransferases, a ST6Gall sialyltransferase or an N-terminal shortened ST6Gall sialyltransferase of at most its first 99 residues.

Legaingneur et al teach full length human α -2,6-sialyltransferases such as a ST6Gall sialyltransferase as well as N-terminal truncated ST6Gall sialyltransferase where the N terminus first 99 residues up to 100 were deleted for in vitro sialylation of hTSH (see entire document, page 21612, col. 2, page 21609, Scheme 1, in particular). The various truncated forms of

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ST6Gall sialyltransferase were expressed in COS cells (see page 21613, in particular). Full-length and truncated forms of the reference enzymes have no difference in substrate recognition and do not alter enzyme folding and activity (see abstract, in particular). Progressive truncation of the N terminus demonstrated that the catalytic domain can proceed with sialic acid transfer with increased efficiency until 80 amino acids are deleted (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute α 2,3 sialyltransferase in the CHO cells of Szudlinski et al for the human α 2,6-sialyltransferase or N-terminal truncation variants thereof up to the first 99 amino acids as taught by Legaingneur et al to limit sialylation-dependent heterogeneity in the hTSH bioactivity as taught by Szudlinski et al in the method of screening glycoform specific antibodies using recombinant TSH as taught by Papandreou et al, Kashiwai et al, Schaaf et al, and Szkudlinski et al.

One of ordinary skill in the art would have been motivated with the expectation of success to substitute α 2,3 sialyltransferase for human α 2,6-sialyltransferase because full length human α -2,6-sialyltransferases such as a ST6Gall sialyltransferase as well as N-terminal truncated ST6Gall sialyltransferase show no difference in substrate recognition and do not alter enzyme folding and activity as taught by Legaingneur et al (see abstract, in particular). Further, progressive truncation of the N terminus up to the first 80 amino acids may even increase the efficiency of sialic acid transfer as taught by Legaingneur et al (see abstract, in particular).

18. Claim 113 is rejected under 35 U.S.C. 103(a) as being unpatentable over Papandreou et al (Molecular and Cellular Endocrinology 73: 15-26, 1990; PTO 1449) in view of Kashiwai et al (J Immunological Methods 143: 25-30, 1991; PTO 892), Schaaf et al (Molecular and Cellular Endocrinology 132: 185-194, 1997; PTO 1449), and Szkudlinski et al (Endocrinology 133(4): 1490-1503, 1993; PTO 892) as applied to claims 101, 103-108 and 110-112 mentioned above and further in view of Zerfaoui et al (Eur J Clin Chem Clin Biochem 34: 749-753, 1996; PTO 1449) and Fionnuala et al (Molecular Biotechnology 12: 203-206, 1999; PTO 1449).

The combined teachings of Papandreou et al, Kashiwai et al, Schaaf et al, and Szkudlinski et al have been discussed supra.

The invention in claim 113 differs from the teachings of the references only in that the process of screening glycoform specific antibodies among antibodies elicited against recombinant human TSH wherein the binding of antibodies is determined by sandwich immunoassay such as

ELISA test comprising the steps of fixing a capture antibody from a pool of antibodies that cannot bind to the same glycoprotein at the same time, contacting a first glycoprotein, to the second glycoprotein, or to the glycoforms of the second glycoprotein to said capture antibody to form a capture antibody-glycoprotein binary complex, contacting a tracer antibody and detecting the tracer antibody for measuring the number of ternary complexes.

Zerfaoui et al teach enzyme-linked immunosorbent assay for comparing antibody recognition of highly purified pituitary TSH and recombinant thyrotropin before and after sialic acid removal (see paragraph bridging pages 751 and 752, Caption in Fig 2, in particular).

Fionnuala et al teach sandwich immunoassay for quantifying protein glycoforms where the capture antibody is first attached to a solid phase (see page 203, col. 1, page 204, Fig 1, in particular), then contacting the immobilized antibody with the glycoform of the same glycoprotein of interest to form a capture antibody-glycoprotein binary complex, follows by contacting a second tracer antibody, which is usually labeled such as streptavidin-enzyme conjugate (see page 203, col. 1, Figure 1 at page 204, in particular). The immobilized antibody capture all of the specific protein in the sample and the enzyme labeled antibody or tracer antibody binds to capture antibody-glycoprotein tracer antibody to form a ternary complex and thereby amplify or increase the assay's sensitivity (see page 206, col. 1, in particular). The sandwich immunoassay can be adapted to quantify any proteins' glycoforms by simply substituting the antibody and lectin with specific alternatives (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skilled in the art at the time the invention was made to screen antibodies based on a pool of antibodies that binds to recombinant TSH or glycoform thereof of Papandreou et al, Kashiwai et al, Schaaf et al, and Szkudlinski et al using solid phase sandwich immunoassay as taught by Fionnuala et al or enzyme-linked immunosorbent assay for comparing antibody recognition of highly purified pituitary TSH and recombinant thyrotropin before and after sialic acid removal as taught by Zerfaoui et al.

One of ordinary skill in the art would have been motivated with the expectation of success to use sandwich immunoassay for capturing various glycoform of various glycoprotein because sandwich immunoassay can be adapted to quantify any proteins' glycoforms by simply substituting the antibody and lectin with specific alternatives with increase sensitivity as taught by Fionnuala et al (see abstract, page 206, col. 1, in particular).

One of ordinary skill in the art would have been motivated with the expectation of success to use sandwich immunoassay for comparing antibody recognition of highly purified

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pituitary TSH and recombinant thyrotropin before and after sialic acid removal because it is conventional and known to one of ordinary skill in the art at the time invention was made as taught by Zerfaoui et al.

19. No claim is allowed.
20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.
21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/

Primary Examiner, Art Unit 1644

May 22, 2009